HED DOC. NO. 013616

August 6, 1999

MEMORANDUM

SUBJECT: ***TERBUFOS*** **-** Report of the FQPA Safety Factor Committee

The FQPA safety factor recommendation in this report supercedes that previously reported for terbufos in the FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES dated August 6, 1998.

FROM: Brenda Tarplee, Executive Secretary
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THROUGH: Ed Zager, Chairman
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PC Code: 105001

The FQPA Safety Factor Committee met on July 26, 1999 to reevaluate the hazard and exposure data for terbufos, and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed (1x) in assessing risks resulting from the use of terbufos. The FQPA safety factor recommendation in this report supercedes that previously reported for terbufos in the *FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES* dated August 6, 1998.

I. HAZARD ASSESSMENT

A. Adequacy of Toxicology Database

On November 19, 1998 and July 22, 1999, the HIARC reviewed submitted acute and subchronic neurotoxicity studies with terbufos in rats, respectively, which were previously identified as data gaps. The HIARC determined that these studies were acceptable and therefore, the toxicology database is now adequate for terbufos according to the Subdivision F Guideline requirements for a food-use chemical.

B. Evaluation of Neurotoxicity

In an acute delayed neurotoxicity study, no delayed neurotoxicity was seen in hens given a single oral dose of terbufos at 40 mg/kg. A second administration, at the same dose, was given after a 21-day interval. The HIARC noted that this study did not assess the potential of terbufos to inhibit neurotoxic esterase (NTE) in hens (MRID No. 00037472).

In an acute oral neurotoxicity study in rats, the first indication of a compound-related effect (miosis) detected by the functional observational battery (FOB) was reported at the 0.3 mg/kg and 0.90 mg/kg doses approximately 6 hours after exposure to the test substance in both males and females. In addition to miosis, females at the 0.90 mg/kg dose level showed evidence of excessive salivation, lacrimation, ataxia, stupor, soiled coat, decreased forelimb strength, slightly impaired locomotion, and tremors. These symptoms resolved within the first week after treatment with the test article and were no longer evident at the Day 7 observation period. Gross necropsy examination and histopathology testing of animals that were euthanized at the end of the study revealed no compound-related abnormalities (MRID No. 44672003).

In a subchronic neurotoxicity study in rats, no adverse or treatment-related effects were observed on mortality or clinical signs. The high-dose males displayed slightly decreased body weights throughout the study compared to the controls, but the high-dose females displayed body weights that were comparable to or greater than the controls throughout the study. Body-weight gains were decreased in the high-dose males throughout the study, although the magnitude of the deficit diminished with time. There was no adverse effect on body-weight gain in the females. Food consumption was comparable to/greater than the control in the treated groups [both sexes]. There were no treatment-related effects observed on ophthalmoscopy, and motor activity was comparable among the groups for both sexes throughout the study. There were no significant and treatment-related differences relative to the controls in any of the parameters monitored in the FOB in either sex. No treatment-related macroscopic and microscopic lesions were observed in either sex. Brain weight data were not provided (MRID 44842302).

C. Developmental Toxicity

In a developmental toxicity study pregnant Crl:COBS-CD(SD) rats received oral doses of terbufos in corn oil at 0, 0.05, 0.1 or 0.2 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.2 mg/kg/day (HDT); a LOEL was not established. For developmental toxicity, the NOEL was 0.1 mg/kg/day and the LOEL was 0.2 mg/kg/day based on increases in early fetal resorptions, the number of litters with two or more resorptions, and post-implantation losses. There was no evidence of teratogenicity (MRID No. 00147533).

In a developmental toxicity study, pregnant New Zealand White rabbits were given a single oral dose of terbufos 0, 0.05, 0.10, 0.25 or 0.50 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOEL was 0.1 mg/kg/day and the LOEL was 0.25 mg/kg/day based on decreased body weight gain and increased incidence of soft stools. For developmental toxicity, the NOEL was 0.25 mg/kg/day and the LOEL was 0.5 mg/kg/day based on a slight reduction in fetal body weight and an increase in resorptions. There was no evidence of teratogenicity (MRID No. 40886301).

D. Reproductive Toxicity

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing terbufos at 0, 0.5, 1 or 2.5 ppm for 9 weeks prior to mating (males and females) as well as during both gestation and lactation. There was no increased sensitivity to pups over the adults. The maternal/offspring NOEL was 1 ppm (0.08-0.09 mg/kg/day) and the LOEL was 2.5 ppm (0.22-0.24 mg/kg/day) based on a decreased body weight gain in females during lactation and lower pup weights during lactation days 14 and 21. For reproductive toxicity, the NOEL was 1 ppm (0.07 mg/kg/day) and the LOEL was 2.5 ppm (0.17 mg/kg/day) based on a decrease in pregnancy rate and male fertility. For cholinesterase inhibition (measured only in adults), the NOEL was 0.5 ppm (0.04 mg/kg/day) and the LOEL was 1 ppm (0.08 mg/kg/day) based on >50% inhibition of plasma cholinesterase activity (MRID No. 43649402).

E. Determination of Developmental Neurotoxicity Study

There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to terbufos. These include acceptable developmental toxicity studies in rats and rabbits, as well as, a 2-generation reproduction studies in rats. There was no evidence of abnormalities to the fetus or to the fetal nervous system in the pre- and post-natal studies. Additionally, no treatment-related neuropathology was seen after acute and subchronic exposure to rats. Based on the weight-of-evidence, the HIARC determined that a developmental neurotoxicity study in rats is not required for terbufos.

F. Determination of Susceptibility

Upon re-evaluation of the hazard and exposure data bases for terbufos, the FQPA Safety Factor Committee requested clarification of HIARC's conclusion that "no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to Terbufos and comparable NOELs were established for adults and offspring", specifically the findings reported in the developmental study in rats. The clarifications follow:

- The HIARC report of the May 12, 13, and 14, 1998 meeting was erroneous in that the maternal and developmental LOAELs and NOAELs were not at the same dose level in the developmental toxicity study in rats. However, there is not a concern for the apparent quantitative increased susceptibility since oral studies with Terbufos demonstrate that had cholinesterase been measured, inhibition would most likely been observed in the dams at the developmental LOAEL (0.2 mg/kg/day): Cholinesterase inhibition occurred after a single oral dose of 0.3 mg/kg/day in the acute neurotoxicity study in rats (MRID No: 44672003); and after repeated oral dosing at 0.37 mg/kg/day in the subchronic neurotoxicity study in rats (MRID No. 44842302).

- The developmental LOAEL was conservatively established for fetal effects seen at the 0.2 mg/kg/day dose level. The results of the range-finding study indicate that this is approaching a dose that would cause severe maternal toxicity: death occurred in the dams in this study at 0.4 mg/kg/day.

- Although the HIARC did not dispute the dose level at which the developmental LOAEL was established, it is noted that the increase in resorptions observed in the rat developmental study was minimal with no dose response and no statistical significance when compared to concurrent controls. Additionally, the increase in resorptions at 0.2 mg/kg/day in the rat developmental study was contrary to the results in the range-finding study wherein a decrease in resorptions was observed at the 0.2 mg/kg/day dose level. Also at the high dose, the incidence of post-implantation loss was only minimally outside of the historical control range for the performing laboratory (1.3 vs. 1.2). The number of live fetuses per dam at cesarean section for the 0.2 mg/kg/day dose group was also found not to be significantly decreased.

In summary, a weight-of-evidence analysis of the toxicity data base for terbufos indicates there is no concern for quantitative or qualitative increased susceptibility to rats or rabbits following pre- /or postnatal exposure in the developmental and reproductive toxicity studies (*Memorandum:* B. Tarplee to W. Hazel dated August 2, 1999; HED Doc. No.013598).

G. Data Gaps

None.

II. EXPOSURE ASSESSMENTS

A. Dietary (Food) Exposure Considerations

(*Correspondence:* W. Hazel to B. Tarplee and J. Holmes dated July 16, 1999)

Terbufos is a systemic insecticide/nematicide. Permanent tolerances have been established for the combined residues of terbufos and its cholinesterase-inhibiting metabolites in/on corn, sorghum, sugar beets, and bananas at levels ranging from 0.025 ppm to 0.5 ppm [40 CFR §180.352].

Terbufos is used on bananas which are considered to be highly consumed by infants and children (1993 NAS report, Pesticides in the Diets of Infants and Children).

Residue data sources available for terbufos include: field trial data; Pesticide Data Program (PDP) monitoring data; and FDA surveillance data. However, only field trial data included all six cholinesterase-inhibiting residues of concern (terbufos and its sulfone and sulfoxide; and the O-analog of terbufos and its sulfone and sulfoxide). Information on percent of crop treated (%CT) is also available for terbufos from the Biological and Economic Analysis Division (BEAD) for this pesticide.

There were no detectable residues of parent terbufos reported in the available field trial, PDP, or FDA data for corn and sorghum. In banana field trials, detectable residues were found in some samples at levels ranging from 0.01 ppm - 0.025 ppm.

The chronic dietary food exposure analysis for terbufos at the time of this review, was refined using available anticipated residue data from field trials and percent crop treated information which also results in a more realistic estimate of dietary food exposure.

For acute dietary food risk assessment, a Monte Carlo probabilistic analysis has been submitted to the Agency and reviewed. Additionally, the Agency has conducted its own probabilistic assessments. Probabilistic techniques can enhance risk estimates by more fully incorporating the available information on the range of possible values that an input variable could take, and weighting these values by their probability of occurrence. The resulting output of a probabilistic determination is a distribution of risk values with probability assigned to each estimated risk which in turn, results in a more realistic reflection of the expected exposure.

B. Dietary (Drinking Water) Exposure Considerations

(*Correspondence:* J. Breithaupt to B. Tarplee and J. Holmes dated July 19, 1999)

The environmental fate data base for parent terbufos is complete. Parent terbufos degrades relatively quickly in soil to form the sulfoxide and sulfone degradates. The fate data base for the terbufos sulfoxide and sulfone degradates is incomplete, but available data indicate that they are more persistent and mobile than parent terbufos.

All monitoring to date has focused on the parent compound. New USGS monitoring is just beginning that will include terbufos and the soil/water degradates of concern (terbufos sulfone and sulfoxide). Monitoring data from a ground water study conducted in Iowa for the use of terbufos on corn were determined to be unacceptable and should not be used in drinking water risk assessments.

Since there is inadequate monitoring data available for terbufos for both ground water and surface water, all estimated environmental concentrations (EECs) are calculated using models:

For surface water, the PRZM-EXAMS model will be used for parent and degradates accounting for the formation and decline rates of these degradates. Until the new modeling is completed, the old numbers for parent only will be used as a lower bound. When monitoring data are available, these will be considered.

For ground water, the SCI-GROW2 model incorporates half-lives for the residues of concern, the lowest mobility constant for terbufos sulfoxide and sulfone, and the maximum application rate for each crop.

The Safety Factor Committee members expressed concern that the estimated environmental concentrations for surface water did not currently include the terbufos sulfone and terbufos sulfoxide. The Committee recommended that worst-case assumptions be made in modeling these degradates so that the drinking water risk assessments do not underestimate exposure from the cholinesterase-inhibiting metabolites of concern (terbufos sulfone and sulfoxide).

C. Residential (Non-Occupational) Exposure Considerations

Terbufos is not currently registered for residential use.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

Previously for terbufos, the FQPA safety factor recommendation was 3x due to the data gaps for the acute and subchronic neurotoxicity studies (*FQPA Safety Factor Recommendations for the Organophosphates* dated August 6, 1998). These data requirements have now been satisfied and therefore, the Committee recommends that the FQPA safety factor be **removed (1x)** for terbufos.

B. Rationale for Selection of the FQPA Safety Factor

The FQPA Safety factor Committee concluded that the safety factor could be removed (1x) since:

1. The toxicology database is now complete (previous data gaps have been satisfied);

2. There is no indication of increased susceptibility of young rats or rabbits to terbufos. In the developmental and reproduction toxicity studies, effects in the fetuses/offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity;

3. The HIARC determined that a developmental neurotoxicity study in rats is not required;

4. The dietary food exposure assessment does not underestimate the potential exposure to infants and children from residues in food;

5. The dietary water exposure assessment should include worst-case assumptions in modeling the degradates of concern (terbufos sulfone and sulfoxide) so that the drinking water risk assessments do not underestimate exposure from the cholinesterase-inhibiting metabolites; and

6. No exposure is expected to infants and children from residential (non-occupational) sources.